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(54) Title: COSMETIC FOR SKIN WHITENING CONTAINING ACYL SUBSTITUTED DERIVATIVES OF GLUCOSE OR SUCROSE

(57) Abstract: The present invention relates to cosmetic for skin whitening containing glucose derivatives having 3≈5 of acyl groups and/or sucrose derivatives having 6≈8 of acyl groups as an effective component. Glucose acyl substituted derivatives and sucrose acyl substituted derivatives are easy to synthesize, have no side effects on skin, and have a superior effect to inhibit pigmentation on skin by restraining melanin from being generated. Accordingly, the cosmetic containing the same material is usefully used for skin whitening.

COSMETIC FOR SKIN WHITENING CONTAINING ACYL SUBSTITUTED DERIVATIVES OF GLUCOSE OR SUCROSE

TECHNICAL FIELD

The present invention relates to cosmetic for skin whitening, and more particularly, to cosmetic for skin whitening containing acyl substituted derivatives of glucose or sucrose which are easy to synthesize, have no side effects on skin, and have a superior effect to inhibit pigmentation on skin by restraining melanin from being generated.

BACKGROUND ART

Most people want to have white and fine skin. The color of human skin is determined by the density and the distribution of melanin inside skin and affected by the environmental or physiological factor such as ultraviolet rays of the sun, fatigue, or stress as well as the genetic factor. Melanin is made through the following steps: first, enzyme tyrosinase affects on a kind of amino acid, tyrosine to change the same into DOPA or dopaquinone and then the same goes through non-enzymatic oxidation reaction. However, the mechanism that derives melanin synthesis, which is a step before tyrosinase affects, is not clarified in detail though the process through which melanin is made is disclosed.

When the melanin synthesis is excessively performed inside skin, the tone of skin darkens and chloasma and freckles can be generated. Accordingly, when the melanin synthesis inside skin is inhibited, the skin whitening is possible, plus

hyperpigmentation such as chloasma, freckles, etc. due to ultraviolet rays or hormonic and genetic factors can be improved.

Conventionally, the skin whitening is tried by mixing material having inhibition function against tyrosinase such as hydroquinone, ascorbic acid, kojic acid, or glutathione with cosmetic such as essence or ointment for external use. However, although hydroquinone shows a prescribed effect of whitening, the mixture amount of the same should be restricted to minimum since the same seriously irritates skin, in case of ascorbic acid, since the same is easy to be oxidized, cosmetic mixed with the same has problems of discoloration and change of scent, and in case of kojic acid, the same is restricted to be used since the same is unstable. Further, thiol compound such as glutathione or cysteine has a peculiar bad smell and low absorptiveness to skin.

On the other hand, it is reported that an plant extract such as licorice extract or white mulberry extract(Fragrance.J., 6, 59 (1990)) has superior effect of skin whitening. However, in case of using such a plant extract, it is difficult to maintain the uniformity of products since the same considerably differs in its effect according to the growing area of plant, plus the examination on skin irritativeness and stability is not sufficient. In addition, in case of kazinol F extracted from paper mulberry(Chem. Phar. Bull., 34(5) 1968 (1986), Cosmetics & Toiletries, 101, 51(1995)), sucrose 4,7,8,11,12-pentaisovalerate(Kor. J. Pharmacogn. 21(2) : 168~173 (2000)) extracted from Euphorbia lathyris , etc., it is difficult to commercialize the same since the same is not easy to synthesize and has low synthetic yield.

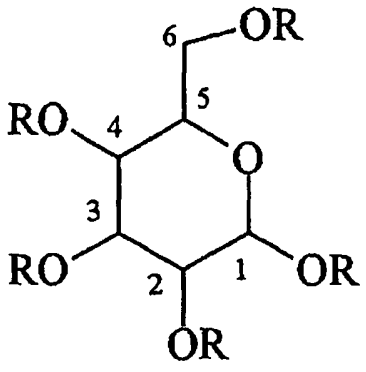
DISCLOSURE OF THE INVENTION

Accordingly, an object of the present invention is to overcome the above-mentioned and to provide cosmetic for skin whitening, which is easy to synthesize, has no side effects on skin, and has a superior effect to inhibit pigmentation on skin by restraining melanin from being generated.

The detailed description about the cosmetic according to the present is provided hereinafter.

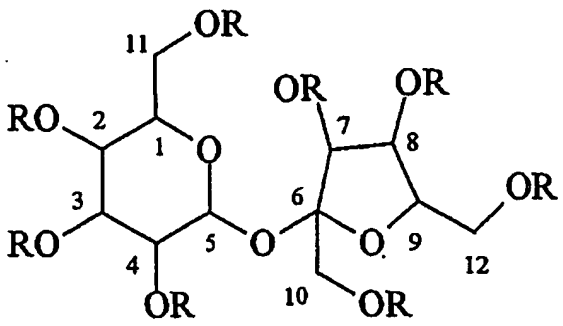
The present invention provides cosmetic for skin whitening containing an effective amount of one selected from a group comprising glucose acyl substituted derivatives represented by the following chemical formula 1, sucrose acyl substituted derivatives represented by the following chemical formula 2, and mixtures of those.

[Chemical Formula 1]



In the above chemical formula 1, R means hydrogen atom or acyl group having the number of carbon of 3~6. The acyl group is linear chain type or branched chain type and the number of acyl group substituted is 3 to 5.

[Chemical Formula 2]

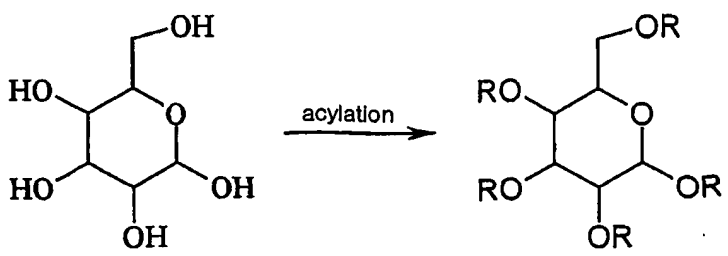


In the above chemical formula 2, R means hydrogen atom or acyl group having the number of carbon of 3~6. The acyl group is linear chain type or branched chain type and the number of acyl group substituted is 6 to 8.

Such glucose acyl substituted derivatives or sucrose acyl substituted derivatives according to the present invention is easy to synthesize and have superior effect of restraining the generation of melanin and whitening skin without side effects on skin. Accordingly, when the same compound is added to cosmetic such as ointment for external use, essence, or cream, the high-potency of skin whitening without any special side effects can be obtained.

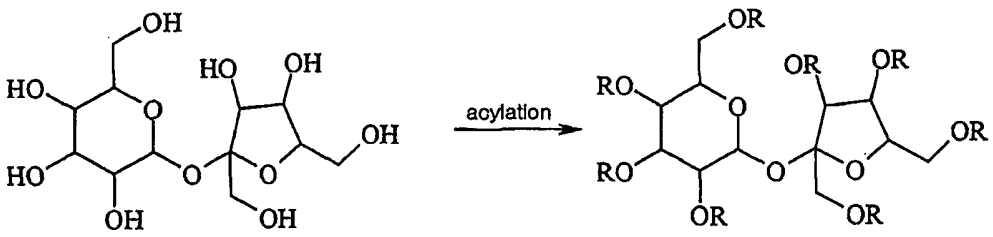
Glucose acyl substituted derivatives or sucrose acyl subustituted derivatives according to the present invention may be manufactured by using the conventionally known synthetic method according to the following reaction formula, respectively(Refer to Synthesis, 453 (1986)).

[Reaction Formula 1]



In the above reaction formula 1, R means hydrogen atom or acyl group having the number of carbon of 3~6. The acyl group is linear chain type or branched chain type and the number of acyl group substituted is 3 to 5.

[Reaction Formula 2]



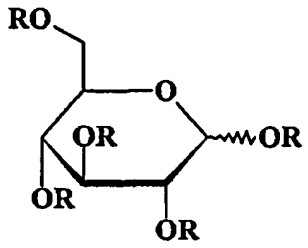
In the above reaction formula 2, R means hydrogen atom or acyl group having the number of carbon of 3~6. The acyl group is linear chain type or branched chain type and the number of acyl group substituted is 6 to 8.

Glucose and sucrose acyl substituted derivatives synthesized according to the above reaction formulas have a different number of acyl group substituted according to reaction temperature, reaction time, whether or not catalyst is used. Glucose acyl substituted derivatives having 3~5 of acyl group substituted and sucrose acyl substituted derivatives having 6~8 of acyl group substituted have superior effect of restraining generation of melanin.

When the acylation reaction that glucose and sucrose acyl substituted derivatives are synthesized is performed, DMF(dimethyl formamide), DMSO (dimethyl sulfoxide), or pyridine may be used as a solvent and pyridine is preferable. In addition, as anhydrous acid used for acylation reaction, anhydrous propionic aicd, anhydrous butylic acid, anhydrous isobutylic acid, anhydrous valeric acid, anhydrous isovaleric acid, anhydrous 2-ethylbutyric acid, anhydrous hexanoic acid, or anhydrous 2-methylvaleric acid may be used.

Glucose acyl substituted derivatives synthesized according to the above reaction formula 1 may be separated and refined into glucose 1,2,3,4,6-penta-O-isovalerate, glucose 1,2,3,4-tetra-O-isovalerate, glucose 1,2,4,6-tetra-O-isovalerate, glucose 1,2,3,6-tetra-O-isovalerate, glucose 1,3,6-tri-O-isovalerate, glucose 1,2,3,4,6-penta-O-isobutylate, glucose 1,2,3,4-tetra-O-isobutylate, glucose 1,2,4,6-tetra-O-isobutylate, glucose 1,2,3,6-tetra-O-isobutylate, glucose 1,3,6-tri-O-isobutylate, etc. Among them, an α and β types of compound, glucose 1,2,3,4,6-penta-O-isovalerate represented by the following chemical formula 3 has superior effect of skin whitening.

[Chemical Formula 3]



In the above chemical formula 3, R means  .

In addition, sucrose acyl substituted derivatives synthesized according to the above reaction formula 2 may be separated and refined into sucrose 2,3,4,7,8,10,11,12-octa-O-isovalerate, sucrose 2,4,7,8,10,11,12-hepta-O-isovalerate, sucrose 3,7,8,10,11,12-hexa-O-isovalerate, sucrose 2,3,4,7,8,10,11,12-octa-O-isobutylate, sucrose 2,4,7,8,10,11,12-hepta-O-isobutylate, sucrose 3,7,8,10,11,12-hexa-O-isobutylate, etc.

Such glucose or sucrose acyl substituted derivatives may be used by being mixed with various cosmetic such as ointment for external use, cream,

softening lotion, essence, pack, nutritious lotion, etc. The content of glucose acyl substituted derivatives and/or sucrose acyl substituted derivatives contained in the cosmetic according to the present invention is preferably 0.0001 to 15 weight% on the basis of total weight, and more preferably 0.001 to 10weight%.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The detailed description of the present invention referring to the embodiments is provided hereinafter. However, the embodiments according to the present invention can be modified in various ways and should not be understood to be restricted to the embodiments described below. The embodiments of the present invention are provided to more clearly and easily describe the present invention to a person who has standard knowledge in this technical area.

Synthetic Example 1 (Synthetic example of glucose isovalerate derivative)

5g(27.8mmol) of glucose is put in a two-necked round bottom flask and 50ml of pyridine is added to dissolved completely in water bath. The solution maintained at 0°C into which 5.5 equivalent weight of anhydrous isovaleric acid is slowly dropped is agitated for 3 hours and then 5.5 equivalent weight of anhydrous isovaleric acid is additively dropped. Next, the reaction is performed for 30 hours at the temperature raised up to 25°C. Then, the reaction is stopped by adding 150ml of methanol, the solvent is completely removed under reduced pressure, and 300ml of chloroform is added. The product obtained above is washed twice

respectively by adding 250ml of aqueous solution of 1N hydrogen chloride and 250ml of saturated aqueous solution of sodium bicarbonate. A layer of chloroform is dried under reduced pressure and then 13.5g of oil is obtained. The obtained oil is separated and refined by using silica column chromatography (ethylacetate/hexane 1:5) and 4.5g(Rf=0.72, yield: 27.0%) of glucose 1,2,3,4,6-penta-O-isovalerate, 0.5g(Rf=0.60, yield: 3.5%) of glucose 1,2,3,4-tetra-O-isovalerate, 2.3g(Rf=0.65, yield: 16.0%) of glucose 1,2,4,6-tetra-O-isovalerate, 0.6g(Rf=0.55, yield: 4.2%) of glucose 1,2,3,6-tetra-O-isovalerate, and 1.2g (Rf=0.43, yield: 10.0%) of glucose 1,3,6-tri-O-isovalerate is respectively obtained thereby.

The above obtained glucose isovalerate derivatives are identified by the Fast Atom Bombardment Mass Spectrometry(FAB-MS, hereinafter) and 300 MHz NMR Spectrometry(^1H, ^{13}C).

glucose 1,2,3,4,6-penta-O-isovalerate

FAB mass : 623.4 $[M+Na]^+$

H-NMR(δ , CDCl3) : 6.36 (1H, d, *J* 3.7 1-α -H), 5.72 (1H, d, *J* 8.3 1-β -H), 5.50 (1H, t, *J* 10.1 3-α -H), 5.28 (1H, t, *J* 9.5 3-β -H), 5.06~5.19 (4H, m, 2,4-α ,β -H), 5.06 (2H, m, 2-α ,β -H) 4.13~4.17 (4H, m, 6-α ,β -H), 4.10 (1H, m, 5-α -H), 3.82 (1H, m, 5-β -H), 2.31-2.13 (20H, m, 5×$CH_2CH(CH_3)_2$) 2.13-2.03 (5H , m 5×$CH_2CH(CH_3)_2$) 1.01-0.9 (60H , m, 4×$CH_2CH(CH_3)_2$)

glucose 1,2,3,4-tetra-O-isovalerate

FAB mass : 539 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.61 (1H, t, *J* 9.5 3-H), 5.20-

5.06 (2H, m, 2,4-H), 3.91 (1H, ddd, *J* 10, 4.5, 2, 5-H) 3.79-3.63 (2H, m, 6-H), 2.30-2.13 (8H, m, 4×$CH_2CH(CH_3)_2$) 2.12-2.04.(4H, m, 4×$CH_2CH(CH_3)_2$) 1.01-0.9 (24H, m, 4×$CH_2CH(CH_3)_2$)

glucose 1,2,3,6-tetra-O-isovalerate

FAB mass : 539 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.39 (1H, t, *J* 10, 3-H), 5.12 (1H, dd, J10 and 3.5, 2-H), 4.61-4.52 (2H, m, 6-H) 3.99 (1H, ddd, J10,4 and 2.5, 5-H), 3.60(1H, t, *J* 10, 4-H) 2.32-2.14 (8H, m, 4×$CH_2CH(CH_3)_2$) 2.12-2.02.(4H , m, 4 ×$CH_2CH(CH_3)_2$) 1.01-0.9 (24H , m, 4×$CH_2CH(CH_3)_2$)

glucose 1,2,4,6-tetra-O-isovalerate

FAB mass : 539 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.33 (1H, d, *J* 3.6 1-H), 5.05-4.99 (2H, m, 2,4-H), 4.18 (1H, dd, J10 and 3.5, 2-H), 4.61-4.52 (2H, m, 6-H) 3.99 (1H, ddd, J10,4 and 2.5, 5-H), 3.60(1H, t, *J* 10, 4-H) 2.32-2.14 (8H, m, 4×$CH_2CH(CH_3)_2$) 2.12-2.02.(4H , m, 4×$CH_2CH(CH_3)_2$) 1.01-0.9 (24H , m, 4×$CH_2CH(CH_3)_2$)

glucose 1,3,6-tri-O-isovalerate

FAB mass : 456 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.01 (1H, t, *J* 9.8, 3-H), 4.53 (2H, m, 6-H), 3.98 (2H, ddd, , J9.8, 4 and 2.5, 5-H) 3.58 (1H, m, 4-H), 3.60(1H, t, *J* 9.8, 2-H) 2.30-2.13 (8H, m, 4×$CH_2CH(CH_3)_2$) 2.12-2.03.(3H, m, 3×$CH_2CH(CH_3)_2$) 1.00-0.89 (18H , m, 3×$CH_2CH(CH_3)_2$)

Synthetic Example 2 (Synthetic example of glucose isobutylate derivative)

3.5g(Rf=0.80, yield: 27.5%) of glucose 1,2,3,4,6-penta-O-isobutylate, 0.4g(Rf=0.70, yield: 27.0%) of glucose 1,2,3,4-tetra-O-isobutylate, 2.7g(Rf=0.68, yield: 23.0%) of glucose 1,2,4,6-tetra-O-isobutylate, 0.61g(Rf=0.73, yield: 27.0%) of glucose 1,2,3,6-tetra-O-isobutylate and 0.59g(Rf=0.65, yield: 5.0%) of glucose 1,3,6-tri-O-isobutylate is respectively obtained by synthesizing, separating and refining with the same method as that of the synthetic example 1 except that anhydrous isobutylic acid instead of anhydrous isovaleric acid is used.

The above obtained glucose isobutylate derivatives are identified by using the same spectrometry as that of the synthetic example 1.

glucose 1,2,3,4,6-penta-O-isobutylate

FAB mass : 558 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.33 (1H, d, *J* 3.7 1-H), 5.49 (1H, t, *J* 9.5 3-H), 5.13 (1H, t, *J* 9.9 4-H), 5.06 (1H, dd, *J* 9.9 and 3.7, 2-H) 4.12 (2H, m, 6-H), 4.06 (1H, m, 5-H), 2.75-2.42 (5H, m, $5\times CH_2(CH_3)_2$) 1.29-1.10 (30H , m, $5\times CH(CH_3)_2$)

glucose 1,2,3,4-tetra-O-isobutylate

FAB mass : 488 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.61 (1H, t, *J* 9.5 3-H), 5.20-5.06 (2H, m, 2,4-H), 3.91 (1H, ddd, *J* 10, 4.5, 2, 5-H) 3.79-3.63 (2H, m, 6-H), 2.73-2.40 (4H, m, $4\times CH_2(CH_3)_2$) 1.28-1.07 (24H , m, $4\times CH(CH_3)_2$)

glucose 1,2,3,6-tetra-O-isobutylate

FAB mass : 488 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.39 (1H, t, *J* 10, 3-H), 5.12 (1H, dd, J10 and 3.5, 2-H), 4.61-4.52 (2H, m, 6-H) 3.99 (1H, ddd, J10,4 and 2.5, 5-H), 3.60(1H, t, *J* 10, 4-H) 2.76-2.40 (4H, m, 4×$CH_2(CH_3)_2$) 1.31-1.11 (24H , m, 4× $CH(CH_3)_2$)

glucose 1,2,4,6-tetra-O-isobutylate

FAB mass : 488 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.33 (1H, d, *J* 3.6 1-H), 5.05-4.99 (2H, m, 2,4-H), 4.18 (1H, dd, J10 and 3.5, 2-H), 4.61-4.52 (2H, m, 6-H) 3.99 (1H, ddd, J10,4 and 2.5, 5-H), 3.60(1H, t, *J* 10, 4-H) 2.32-2.14 (8H, m, 4×$CH_2CH(CH_3)_2$) 2.12-2.02 (4H , m, 4×$CH_2CH(CH_3)_2$) 1.01-0.9 (24H , m, 4×$CH_2CH(CH_3)_2$)

glucose 1,3,6-tri-O-isobutylate

FAB mass : 418 $[M+Na]^+$

H-NMR (δ , CDCl3) : 6.35 (1H, d, *J* 3.6 1-H), 5.01 (1H, t, *J* 9.8, 3-H), 4.53 (2H, m, 6-H), 3.98 (2H, ddd, , J9.8, 4 and 2.5, 5-H) 3.58 (1H, m, 4-H), 3.60(1H, t, *J* 9.8, 2-H) 2.30-2.13 (6H, m, 3×$CH_2CH(CH_3)_2$) 2.12-2.03.(4H, m, 3×$CH_2CH(CH_3)_2$) 1.00-0.89 (18H, m, 3$CH_2CH(CH_3)_2$)

Synthetic Example 3 (Synthetic example of sucrose isovalerate derivative)

12.3g of oil is obtained by performing synthesis with the same method as that of the synthetic example 1 except that sucrose instead of glucose is put and the agitating temperature changes into 80°C. The obtained oil is separated and

refined by using silica column chromatography(ethylacetate/hexane 1:6) and 2.3g(Rf=0.83, yield: 15.8%) of sucrose 2,3,4,7,8,10,11,12-octa-O-isovalerate, 1.8g(Rf=0.70, yield: 13.4%) of sucrose 2,4,7,8,10,11,12-hepta-O-isovalerate and 1.3g(Rf=0.62, yield: 10.6%) of sucrose 3,7,8,10,11,12-hexa-O-isovalerate is respectively obtained thereby.

The above obtained sucrose isovalerate derivatives are identified by using the same spectrometry as that of the synthetic example 1.

sucrose 2,3,4,7,8,10,11,12-octa-O-isovalerate

FAB mass : 1014 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.46 (1H, m, 5-H), 5.42 (1H, d, J 3.9, 7-H), 5.35 (1H, t, J 8, 8-H), 4.83 (1H, t, J 9.9, 2-H), 4.80 (1H, m, 4-H), 4.51 (1H, t, J 9.9 3-H), 4.21 (2H, m, 12-H), 4.13 (1H, m, 1-H), 4.10 (2H, m, 11-H), 4.06 (1H, m, 9-H), 3.95 (1H, m, 5-H), 2.19-2.10 (16H, m, $8\times CH_2CH(CH_3)_2$) 2.02-1.96(8H, m, $8\times CH_2CH(CH_3)_2$, 0.90-0,7 (48H , m, $4\times CH_2CH(CH_3)_2$)

sucrose 2,4,7,8,10,11,12-hepta-O-isovalerate

FAB mass : 953 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.47 (1H, m, 5-H), 5.43 (1H, d, J 3.9, 7-H), 5.35 (1H, t, J 8, 8-H), 4.83 (1H, t, J 9.9, 2-H), 4.83 (1H, m, 4-H), 4.22 (2H, m, 12-H), 4.13 (1H, m, 1-H), 4.12 (2H, m, 11-H), 4.08 (1H, m, 9-H), 3.95 (2H, m, 10-H), 3.84 (1H, t, J 9.9 3-H), 2.19-2.10 (14H, m, $4\times CH_2CH(CH_3)_2$) 2.02-1.96 (7H , m, $7\times CH_2CH(CH_3)_2$) 0.91-0,75 (42H , m, $7\times CH_2CH(CH_3)_2$)

sucrose 3,7,8,10,11,12-hexa-O-isovalerate

FAB mass : 869 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.45-5.46 (2H, m, 5,7-H), 5.42 (1H, t, J 9.9, 8-H), 5.00 (1H, t, J 8, 3-H), 4.51 (1H, m, 11-H), 4.37 (2H, m, 12-H), 4.36-4.21 (4H, m, 10, 11,12-H), 4.17 (1H, m, 9-H), 4.05 (1H, d, J3.8, 1-H), 3.57 (1H, m, 4-H), 3.39 (1H, t, J9.9, 3-H), 2.19-2.10 (12H, m, $6\times CH_2CH(CH_3)_2$) 2.02-1.96 (7H , m, $6\times CH_2CH(CH_3)_2$) 0.91-0,75 (42H , m, $6\times CH_2CH(CH_3)_2$)

Synthetic Example 4 (Synthetic example of sucrose isobutylate derivative)

12.8g of oil is obtained by performing synthesis with the same method as that of the synthetic example 3 except that anhydrous isobutylic acid instead of anhydrous isovaleric acid is used. The obtained oil is separated and refined by using silica column chromatography(ethylacetate/hexane 1:6) and 2.0g(Rf=0.83, yield: 16.8%) of sucrose 2,3,4,7,8,10,11,12-octa-O-isobutylate, 1.5g(Rf=0.70, yield: 10.4%) of sucrose 2,4,7,8,10,11,12-hepta-O-isobutylate and 1.2g(Rf=0.62, yield: 10.1%) of sucrose 3,7,8,10,11,12-hexa-O-isobutylate is respectively obtained thereby.

The above obtained sucrose isobutylate derivatives are identified by using the same spectrometry as that of the synthetic example 1.

sucrose 2,3,4,7,8,10,11,12-octa-O-isobutylate

FAB mass : 925 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.46 (1H, m, 5-H), 5.39 (1H, d, J 3.9, 7-H), 5.32 (1H, t, J 8, 8-H), 4.82 (1H, t, J 9.8, 2-H), 4.81 (1H, m, 4-H), 4.53 (1H, t, J 9.8 3-H),

4.22 (2H, m, 12-H), 4.12 (1H, m, 1-H), 4.11 (2H, m, 11-H), 4.07 (1H, m, 9-H), 3.95 (1H, m, 5-H), 2.78-2.41 (8H, m, 8×$CH_2(CH_3)_2$) 1.20-1.08 (24H , m, 8× $CH(CH_3)_2$)

sucrose 2,4,7,8,10,11,12-hepta-O-isobutylate

FAB mass : 855 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.49 (1H, m, 5-H), 5.44 (1H, d, J 3.9, 7-H), 5.34 (1H, t, J 8, 8-H), 4.85 (1H, t, J 9.9, 2-H), 4.82 (1H, m, 4-H), 4.21 (2H, m, 12-H), 4.12 (1H, m, 1-H), 4.10 (2H, m, 11-H), 4.08 (1H, m, 9-H), 3.95 (2H, m, 10-H), 3.82 (1H, t, J 9.9 3-H), 2.19-2.10 (14H, m, 7×$CH_2CH(CH_3)_2$) 2.76-2.40 (7H, m, 7×$CH_2(CH_3)_2$) 1.31-1.11 (42H, m, 7×$CH(CH_3)_2$)

sucrose 3,7,8,10,11,12-hexa-O-isobutylate

FAB mass : 785 $[M+Na]^+$

H-NMR (δ , CDCl3) : 5.45-5.46 (2H, m, 5,7-H), 5.42 (1H, t, J 9.9, 8-H), 5.00 (1H, t, J 8, 3-H), 4.51 (1H, m, 11-H), 4.37 (2H, m, 12-H), 4.36-4.21 (4H, m, 10, 11,12-H), 4.17 (1H, m, 9-H), 4.05 (1H, d, J3.8, 1-H), 3.57 (1H, m, 4-H), 3.39 (1H, t, J9.9, 3-H), 2.76-2.40 (6H, m, 6×$CH_2(CH_3)_2$) 1.31-1.11 (36H, m, 6×$CH(CH_3)_2$)

Experimental Example

The whitening effect in a cellular level is tested by adding glucose acyl substituted derivatives and sucrose acyl substituted derivatives compound obtained according to the synthetic examples 1 to 4 and hydroquinone aqueous solution to a culture fluid of B-16 mouse melanoma cell(Lotan R., Lotan D. Cancer

Res. 40:3345-3350, 1980). The final concentrations of the mixture of synthesized compound according to the synthetic examples 1 to 4, each compound separated and refined, and hydroquinone are set according to the concentrations described in tables 1 to 4 and the mixture, each compound and hydroquinone are respectively added to the culture medium of B-16 mouse melanoma cell and the cells are cultured for 3 days. The cultured cells are treated by trypsin and separated from the culture plate. Then, the cells are centrifuged to extract melanin.

1ml of sodium hydroxide solution(1N of concentration) is added to the above-mentioned extract and the mixture is boiled for 10 minutes to melt melanin. Then, the absorbancy of melanin is measured at 400mn by a spectrophotometer and the amount of generated melanin is indicated by the absorbancy per unit number of cell(10^6 cell). Further, the inhibition rate(%) is calculated by using the melanin generation amount of a comparative group is described in tables 1 to 4.

Each compound obtained by the separating and refining treatment according to the synthesis examples 1 to 4 is described as follows.

glucose 1,2,3,4,6-penta-O-isovalerate : Glu-5-iV

glucose 1,2,3,4-tetra-O-isovalerate : Glu-4-iV-1

glucose 1,2,4,6-tetra-O-isovalerate : Glu-4-iV-2

glucose 1,2,3,6-tetra-O-isovalerate : Glu-4-iV-3

glucose 1,3,6-tri-O-isovalerate : Glu-3-iV

glucose 1,2,3,4,6-penta-O-isobutylate : Glu-5-iB

glucose 1,2,3,4-tetra-O-isobutylate : Glu-4-iB-1

glucose 1,2,4,6-tetra-O-isobutylate : Glu-4-iB-2

glucose 1,2,3,6-tetra-O-isobutylate : Glu-4-iB-3

glucose 1,3,6-tri-O-isobutylate : Glu-3-iB

sucrose 2,3,4,7,8,10,11,12-octa-O-isovalerate : Su-8-iV

sucrose 2,4,7,8,10,11,12-hepta-O-isovalerate : Su-7-iV

sucrose 3,7,8,10,11,12-hexa-O-isovalerate : Su-6-iV

sucrose 2,3,4,7,8,10,11,12-octa-O-isobutylate : Su-8-iB

sucrose 2,4,7,8,10,11,12-hepta-O-isobutylate : Su-7-iB

sucrose 3,7,8,10,11,12-hexa-O-isobutylate : Su-6-iB

[Table 1]

Testing material	Final concentration (μg/mℓ)	Amount of generated melanin	Inhibition rate(%)
Comparative group	0	0.047±0.004	-
Hydroquinone	1	0.025±0.002	46
	5	Extinct	-
Mixture of glucose isovalerate derivatives(synthetic example 1)	1	0.035±0.002	25
	5	0.029±0.003	38
	20	0.026±0.004	45
Glu-5-iV	1	0.029±0.002	38
	5	0.026±0.002	45
	20	0.015±0.002	68
Glu-4-iV-1	1	0.034±0.002	28
	5	0.029±0.003	38
	20	0.025±0.004	47
Glu-4-iV-2	1	0.032±0.002	32
	5	0.024±0.003	49
	20	0.020±0.002	57
Glu-4-iV-3	1	0.033±0.002	30
	5	0.026±0.003	45
	20	0.022±0.002	53
Glu-3-iV	1	0.035±0.003	25
	5	0.027±0.002	46
	20	0.024±0.004	49

[Table 2]

Testing material	Final concentration (μg/mℓ)	Amount of generated melanin	Inhibition rate(%)
Comparative group	0	0.047±0.004	-

Hydroquinone	1	0.025±0.002	46
	5	Extinct	-
Mixture of glucose isobutylate derivatives(synthetic example 2)	1	0.039±0.002	17
	5	0.030±0.002	36
	20	0.023±0.004	51
Glu-5-iB	1	0.038±0.003	19
	5	0.030±0.002	36
	20	0.022±0.002	53
Glu-4-iB-1	1	0.037±0.002	21
	5	0.029±0.003	38
	20	0.025±0.002	47
Glu-4-iB-2	1	0.035±0.003	25
	5	0.030±0.002	36
	20	0.024±0.002	49
Glu-4-iB-3	1	0.036±0.003	23
	5	0.029±0.003	38
	20	0.022±0.002	53
Glu-3-iB	1	0.038±0.003	19
	5	0.027±0.002	43
	20	0.023±0.004	51

[Table 3]

Testing material	Final concentration (㎍/㎖)	Amount of generated melanin	Inhibition rate(%)
Comparative group	0	0.047±0.003	-
Hydroquinone	1	0.025±0.002	46
	5	Extinct	-
Mixture of sucrose isovalerate derivatives(synthetic example 3)	1	0.037±0.003	21
	5	0.030±0.002	36
	20	0.026±0.004	45
Su-8-iV	1	0.036±0.002	23
	5	0.028±0.002	40
	20	0.024±0.002	49
Su-7-iV	1	0.033±0.002	30
	5	0.026±0.002	45
	20	0.021±0.002	55
Su-6-iV	1	0.035±0.002	25
	5	0.028±0.003	40
	20	0.026±0.002	45

[Table 4]

Testing material	Final concentration (㎍/㎖)	Amount of generated melanin	Inhibition rate(%)
Comparative group	0	0.047±0.003	-

Hydroquinone	1	0.025±0.002	46
	5	Extinct	-
Mixture of sucrose isobutylate derivatives(synthetic example 4)	1	0.038±0.003	21
	5	0.031±0.002	34
	20	0.025±0.004	47
Su-8-iB	1	0.036±0.002	23
	5	0.028±0.002	40
	20	0.024±0.003	49
Su-7-iB	1	0.037±0.002	30
	5	0.027±0.004	45
	20	0.023±0.003	51
Su-6-iB	1	0.035±0.003	25
	5	0.029±0.002	38
	20	0.027±0.002	43

Referring to the tables 1 to 4, glucose acyl substituted derivatives and sucrose acyl substituted derivatives have a very high-potency of restraining the generation of melanin of the cultured mouse melanoma cells by comparison with those of the comparative group. Especially, glucose 1,2,3,4,6-penta-O-isovalerate has superior effect of restraining the generation of melanin. On the other hand, hydroquinone has a high-potency of restraining the generation of melanin, but the same has serious cytotoxicity when the concentration of the same is more than 1μg/ml, so that the experiment is impossible. On the contrary, since glucose acyl substituted derivatives and sucrose acyl substituted derivatives according to the present invention have no cytotoxicity even when those concentrations are 20μg/m, it is possible to make the same have a high-potency of restraining the generation of melanin.

Hereinafter, the effect of inhibiting pigmentation of cosmetic containing glucose acyl substituted derivatives and sucrose acyl derivatives is tested by applying cosmetic such as ointment for external use, cream, softening lotion, nutritious lotion, pack, or essence made by adding glucose acyl substituted derivatives and sucrose acyl substituted derivatives to testees.

Embodiment 1 and comparative example 1

An ointment for external use is manufactured with components and contents as described in table 5.

[Table 5]

Name of material(wt%)	Embodiment 1					Comparative example 1
	a	b	c	d	e	
Glu-5-iV	1	-	-	-	-	-
Glu-4-iV-2	-	1	-	-	-	-
Glu-5-iB	-	-	1	-	-	-
Su-7-iV	-	-	-	1	-	-
Su-7iB	-	-	-	-	1	-
Diethyl sebacate	8	8	8	8	8	8
Spermaceti	5	5	5	5	5	5
Polyoxyethylene oleylether phosphate	6	6	6	6	6	6
Sodium benzoic acid	q.s	q.s	q.s	q.s	q.s	q.s
Vaseline	to 100	To 100	to 100	to 100	to 100	to 100

Embodiment 2 and comparative example 2

A cream is manufactured with components and contents as described in table 6.

[Table 6]

Name of material(wt%)	Embodiment 2					Comparative example 2
	a	b	c	d	e	
Glu-5-iV	0.1	-	-	-	-	-
Glu-4-iV-2	-	0.1	-	-	-	-
Glu-5-iB	-	-	0.1	-	-	-
Su-7-iV	-	-	-	0.1	-	-
Su-7iB	-	-	-	-	0.1	-
Stearic acid	1.0	1.0	1.0	1.0	1.0	1.0
Cetanol	2.0	2.0	2.0	2.0	2.0	2.0
PEG-20	1.0	1.0	1.0	1.0	1.0	1.0
Sorbitan monostearate	1.0	1.0	1.0	1.0	1.0	1.0
Mineral oil	10.0	10.0	10.0	10.0	10.0	10.0
Trioctanoate	5.0	5.0	5.0	5.0	5.0	5.0
Triethanolamine	0.5	0.5	0.5	0.5	0.5	0.5
Carbomer	0.2	0.2	0.2	0.2	0.2	0.2
Glycerin	5.0	5.0	5.0	5.0	5.0	5.0
Propylene glycol	3.0	3.0	3.0	3.0	3.0	3.0
Preservative	q.s	q.s	q.s	q.s	q.s	q.s

Aromatic material	q.s	q.s	q.s	q.s	q.s	q.s
Water	to 100	To 100	To 100	to 100	to 100	to 100

Embodiment 3 and comparative example 3

A softening lotion is manufactured with components and contents as described in table 7.

[Table 7]

Name of material(wt%)	Embodiment 3					Comparative example 3
	a	b	c	d	e	
Glu-5-iV	0.1	-	-	-	-	-
Glu-4-iV-2	-	0.1	-	-	-	-
Glu-5-iB	-	-	0.1	-	-	-
Su-7-iV	-	-	-	0.1	-	-
Su-7iB	-	-	-	-	0.1	-
Ethanol	10.0	10.0	10.0	10.0	10.0	10.0
Polyoxyethylene hardened caster-oil	1.0	1.0	1.0	1.0	1.0	1.0
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2
Glycerin	5.0	5.0	5.0	5.0	5.0	5.0
1,3-buthylene glycol	6.0	6.0	6.0	6.0	6.0	6.0
Aromatic material	q.s	q.s	q.s	q.s	q.s	q.s
Pigments	q.s	q.s	q.s	q.s	q.s	q.s
Water	to 100	to 100	to 100	to 100	to 100	to 100

Embodiment 4 and comparative example 4

An essence is manufactured with components and contents as described in table 8.

[Table 8]

Name of material(wt%)	Embodiment 4					Comparative example 4
	a	b	c	d	e	
Glu-5-iV	0.5	-	-	-	-	-
Glu-4-iV-2	-	0.5	-	-	-	-
Glu-5-iB	-	-	0.5	-	-	-
Su-7-iV	-	-	-	0.5	-	-
Su-7iB	-	-	-	-	0.5	-
Propylene glycol	10.0	10.0	10.0	10.0	10.0	10.0
Glycerin	10.0	10.0	10.0	10.0	10.0	10.0
Sodium hyaluronic acid aquous solution(1%)	5.0	5.0	5.0	5.0	5.0	5.0
Ethanol	5.0	5.0	5.0	5.0	5.0	5.0
Polyoxyethylene hardened	1.0	1.0	1.0	1.0	1.0	1.0

caster-oil						
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1
Carbomer	0.4	0.4	0.4	0.4	0.4	0.4
Aromatic materiall	q.s	q.s	q.s	q.s	q.s	q.s
Water	to 100	to 100	to 100	To 100	to 100	to 100

Embodiment 5 and comparative example 5

A pack is manufactured with components and contents as described in table 9.

[Table 9]

Name of material(wt%)	Embodiment 5					Comparative example 5
	a	b	c	d	e	
Glu-5-iV	0.1	-	-	-	-	-
Glu-4-iV-2	-	0.1	-	-	-	-
Glu-5-iB	-	-	0.1	-	-	-
Su-7-iV	-	-	-	0.1	-	-
Su-7iB	-	-	-	-	0.1	-
Glycerin	5.0	5.0	5.0	5.0	5.0	5.0
Propylene glycol	4.0	4.0	4.0	4.0	4.0	4.0
Polyvinyl alcohol	15.0	15.0	15.0	15.0	15.0	15.0
Ethanol	8.0	8.0	8.0	8.0	8.0	8.0
Polyoxyethylene hardened caster-oil	1.0	1.0	1.0	1.0	1.0	1.0
Polyoxyethylene oleylether phosphate	1.0	1.0	1.0	1.0	1.0	1.0
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2
Aromatic material	q.s	q.s	q.s	q.s	q.s	q.s
Pigments	q.s	q.s	q.s	q.s	q.s	q.s
Water	to 100	to 100	to 100	to 100	to 100	to 100

Embodiment 6 and comparative example 6

A nutritious lotion is manufactured with components and contents as described in table 10.

[Table 10]

Name of material(wt%)	Embodiment 6					Comparative example 6
	a	b	c	d	e	
Glu-5-iV	0.01	-	-	-	-	-
Glu-4-iV-2	-	0.01	-	-	-	-
Glu-5-iB	-	-	0.01	-	-	-
Su-7-iV	-	-	-	0.01	-	-
Su-7iB	-	-	-	-	0.01	-
Polyoxyethylene hardened caster-oil	1.0	1.0	1.0	1.0	1.0	1.0
Methyl paraben	q.s	q.s	q.s	q.s	q.s	q.s
Glycerin	6.0	6.0	6.0	6.0	6.0	6.0
1,3-buthylene glycol	5.0	5.0	5.0	5.0	5.0	5.0
Carbomer	0.2	0.2	0.2	0.2	0.2	0.2
Triethanolamine	0.3	0.3	0.3	0.3	0.3	0.3
Propylene glycol	5.0	5.0	5.0	5.0	5.0	5.0
Ethanol	3.2	3.2	3.2	3.2	3.2	3.2
Carbomer	0.1	0.1	0.1	0.1	0.1	0.1
Pigments	q.s	q.s	q.s	q.s	q.s	q.s
Aromatic material	q.s	q.s	q.s	q.s	q.s	q.s
Water	to 100	to 100	to 100	to 100	to 100	to 100

A process for testing the effect thereof is as follows.

First, an aluminium foil having two rows of six holes with 7mm of diameter is adhered to each forearm of twenty healthy men and women and 60mJ/cm^2 of light is irradiated at 10cm distance from arm by ORIEL solar simulator 1000W. The portion to be irradiated is washed by 70% of ethanol aqueous solution before irradiation. From 3 days before irradiation to 3 weeks after irradiation, the cosmetic according to the embodiments 1 to 6 and that according to the comparative examples 1 to 6 are respectively applied to two rows to be six pairs twice a day. The packs of the embodiment 5 and the comparative examples 5 are removed 15 minutes after application.

After applying the cosmetic according to each embodiment and comparative example as described above, the pigmentation degree is judged with the naked eye and the degrees of restraining pigmentation of the cosmetic

according to each embodiment and that according to each comparative example are compared with each other. Then, the result classifying the degrees thereof into three steps: remarkably effective A, effective B, and no difference C is described in table 11.

[Table 11]

Testing group	Embodiment 1			Embodiment 2			Embodiment 3			Embodiment 4			Embodiment 5			Embodiment 6		
	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C	A	B	C
a(Glu-5-iV)	5	9	6	5	8	7	6	9	5	7	9	4	5	9	6	6	8	6
b(Glu-4-iV-2)	2	8	10	3	9	8	6	6	8	3	8	9	3	6	11	3	8	9
c(Glu-5-iB)	1	9	10	3	8	9	5	5	10	3	9	8	5	8	7	6	7	7
d(Su-7-iV)	3	5	12	5	8	7	5	7	8	3	8	9	4	8	8	4	7	9
e(Su-7-iB)	4	8	8	3	9	8	4	9	7	5	10	5	4	9	7	3	10	7

As shown in table 11, the cosmetics containing glucose acyl substituted derivatives or sucrose acyl substituted derivatives according to the embodiments 1 to 6 have superior effect of skin whitening in comparison with commonly used cosmetics and the cosmetics according to embodiments 1a to 6a containing glucose 1,2,3,4,6-penta-O-isovalerate(Glu-5-iV) have especially superior effect of skin whitening.

INDUSTRIAL APPLICABILITY

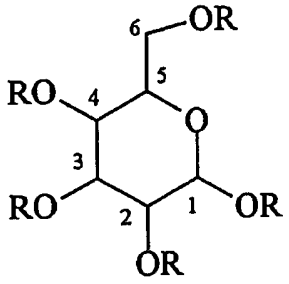
As described above, glucose acyl substituted derivatives and sucrose acyl substituted derivatives according to the present invention are easy to synthesize, have no side effects on skin, and have a superior effect to inhibit pigmentation on skin by restraining melanin from being generated. Accordingly, the cosmetic containing the same material is usefully used for skin whitening.

While the present invention has been described in detail with reference to the preferred embodiments, those skilled in the art will appreciate that various modifications and substitutions can be made thereto without departing from the spirit and scope of the present invention as set forth in the appended claims.

WHAT IS CLAIMED IS:

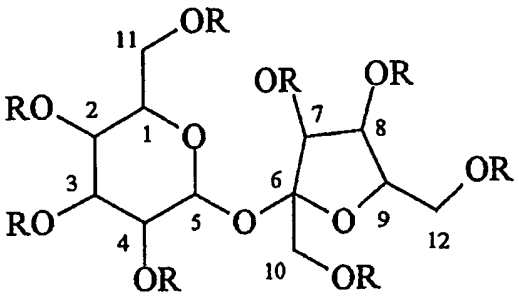
1. Cosmetic for skin whitening containing an effective amount of one selected from a group comprising glucose acyl substituted derivatives represented by the following chemical formula 1, sucrose acyl substituted derivatives represented by the following chemical formula 2, and mixtures of those;

[Chemical Formula 1]



In the above chemical formula 1, R means hydrogen atom or acyl group having the number of carbon of 3~6 and the number of the acyl group is 3 to 5;

[Chemical Formula 2]



In the above chemical formula 2, R means hydrogen atom or acyl group having the number of carbon of 3~6 and the number of the acyl group is 6 to 8.

2. Cosmetic for skin whitening according to claim 1, wherein said

glucose acyl substituted derivative is glucose 1,2,3,4,6-penta-O-isovalerate.

3. Cosmetic for skin whitening according to claim 1, wherein said glucose acyl substituted derivative is one selected from a group comprising glucose 1,2,3,4-tetra-O-isovalerate, glucose 1,2,4,6-tetra-O-isovalerate, glucose 1,2,3,6-tetra-O-isovalerate, glucose 1,3,6-tri-O-isovalerate, glucose 1,2,3,4,6-penta-O-isobutylate, glucose 1,2,3,4-tetra-O-isobutylate, glucose 1,2,4,6-tetra-O-isobutylate, glucose 1,2,3,6-tetra-O-isobutylate, glucose 1,3,6-tri-O-isobutylate, and mixtures of those.

4. Cosmetic for skin whitening according to claim 1, wherein said sucrose acyl substituted derivative is one selected from a group comprising sucrose 2,3,4,7,8,10,11,12-octa-O-isovalerate, sucrose 2,4,7,8,10,11,12-hepta-O-isovalerate, sucrose 3,7,8,10,11,12-hexa-O-isovalerate, sucrose 2,3,4,7,8,10,11,12-octa-O-isobutylate, 2,4,7,8,10,11,12-hepta-O-isobutylate, sucrose 3,7,8,10,11,12-hexa-O-isobutylate, and mixtures of those.

5. Cosmetic for skin whitening according to claim 1, wherein the content of one selected from a group comprising said glucose acyl substituted derivatives, sucrose acyl substituted derivatives, and mixtures of those is 0.0001 to 15 weight% on the basis of total weight of cosmetic.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/02269

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 7/42, A61K 7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

KR JP IPC as above

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5849274 A (BEIERSDORF AG) 15 DEC 1998 see the whole document	1 - 5
A	US 5833960 A (BEIERSDORF AG) 10 NOV 1998 see the whole document	1 - 5

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search	Date of mailing of the international search report
19 APRIL 2002 (19.04.2002)	19 APRIL 2002 (19.04.2002)

Name and mailing address of the ISA/KR	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/02269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5849274 A	15-12-1998	EP 0821946 A	04-02-1998
		DE 19631222 A	12-02-1998
		JP 10067634 A	10-03-1998
US 5833960 A	10-11-1998	EP 0821945 A	04-02-1998
		DE 19631221 A	12-02-1998
		JP 10067633 A	10-03-1998